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## NUTRITIONAL DEFICIENCY AND INFECTION

### I. Influence of Riboflavin or Thiamin Deficiency on Fatal Experimental Pneumococcal Infection in White Mice <sup>1</sup>

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There is a considerable amount of evidence which suggests a relationship between deficient diets and infections in experimental animals.

Webster (1) reported a decrease in mortality in mice infected with *B. enteritidis* following a change in diet. Watson, Wilson, and Topley (2) found that mice fed a diet containing, among other things, dried skimmed milk and oatmeal were more resistant to natural infection with *Bact. typhi murium* than were mice fed on a diet from which the dried skimmed milk was omitted. Church (3) observed that the survival of mice inoculated with *Salmonella enteritidis* was dependent on heredity and nutrition. In addition to much other evidence of a general nature there are also indications of a relationship between infection and specific vitamin deficiencies. Pemberton and Bessey (4) have found a loss of resistance to murine typhus in riboflavin deficient rats, and Badger and Masunaga (5) report that rats on a thiamin deficient diet are more susceptible to rat leprosy than normal rats.

The following investigations were undertaken to determine whether there is a relationship between riboflavin and thiamin deficiency and susceptibility to fatal infection with pneumococcus in mice.

#### EXPERIMENTAL

The strain of mice used in these experiments was a pure strain of Swiss mice obtained from the United States Army Medical School about 4 years ago, and has been maintained at the National Institute of Health by promiscuous mating.

<sup>1</sup> From the Division of Chemotherapy, National Institute of Health.

All studies except those made by paired feeding on litter mates were made on equal numbers of male and female mice. Young mice approximately 4 weeks old, weighing 12 to 15 grams, were employed. The mice were placed in individual glass jars on sawdust in the earlier studies or in individual wire cages with no bedding in later tests.

The basic diet fed throughout these experiments consisted of:

Casein, leached, 70 percent alcohol extracted.....	20 percent
Sucrose (cane sugar).....	71 percent
Wesson oil.....	5 percent
Salt mixture O. and M. 550 modification <sup>2</sup> .....	4 percent
Carotene in oil (7,500 U. S. P. units per gram).....	0.85 mg. per gram of diet.
Vitamin D <sub>2</sub> in propylene glycol (40,000 I. U. per gram).....	0.4 mg. per gram of diet

In addition the vitamins were added in varying amounts as indicated in table 1.

TABLE 1.—Amount of vitamins added per gram of basal diet

Vitamins	Diet number						
	541	541E	541F	597A	597E	597AX	597EX
	Milli-grams	Milli-grams	Milli-grams	Milli-grams	Milli-grams	Milli-grams	Milli-grams
Choline hydrochloride.....	0.3	0.3	0.3	0.3	0.3	0.6	.06
Nicotinic acid.....	.1	.1	.1	.1	.1	.2	.2
Inositol.....	.1	.1	.1	.1	.1	.2	.2
	Micro-grams	Micro-grams	Micro-grams	Micro-grams	Micro-grams	Micro-grams	Micro-grams
Pyridoxine hydrochloride.....	4	4	4	7	7	14	14
Thiamin hydrochloride.....	6.7	6.7	.5	7	7	14	14
Riboflavin.....	6.7	.5	6.7	7	.5	14	5
Calcium pantothenate.....	7	7	7	15	15	30	30

Each group of mice was fed on the various diets for 14 to 21 days in order to allow relative deficiencies to develop in those mice on diets containing restricted amounts of thiamin or riboflavin. At the end of this conditioning period the mice on each diet were divided equally into test and control groups. Mice in the control groups were then lightly etherized and 0.02 to 0.03 ml. of sterile beef infusion broth containing 0.1 ml. sterile defibrinated rabbit blood per 10 ml. of broth was placed on the nose and was allowed to be inhaled. The mice in the test groups were next inoculated with a culture of pneumococcus type I in the following manner: One mouse from each test group on the various diets, taken successively, was lightly etherized and 0.02 to 0.03 ml. of pneumococcus culture was placed on the nose and was allowed to be inhaled. Care was taken that the mouse was under the exact degree of anesthesia to prevent blowing or spattering of the culture. Following the inoculation the mice were observed for

<sup>2</sup> The salt mixture was prepared by the method described by Osborne and Mendel (J. Biol. Chem., 37:572 (1919)) except that the following changes were made: NaF was reduced to 1 percent of the original value and 0.2 gm. CuSO<sub>4</sub> was added.

10 days. Deaths occurring were recorded and cultures of the heart blood were made from representative numbers.

The culture of pneumococcus for inoculation was grown in beef infusion broth, that previously had been found to support good growth of the organism, with 0.1 ml. of defibrinated rabbit blood per 10 ml. of broth for 5 hours at 37° C. If good growth was obtained the organisms were tested for capsule swelling with specific diagnostic serum. Only cultures that showed good capsules were used.

The effect of diet 541, riboflavin deficient diet 541E and thiamin deficient diet 541F on the rate of growth and survival of mice was demonstrated by a 24-day feeding test on 25 males and 25 females on each diet. Mice fed diet 541 gained weight over the period observed in these tests. Whereas the mice fed on diets 541E and 541F, which contained 0.5 microgram per gram of riboflavin and thiamin chloride,

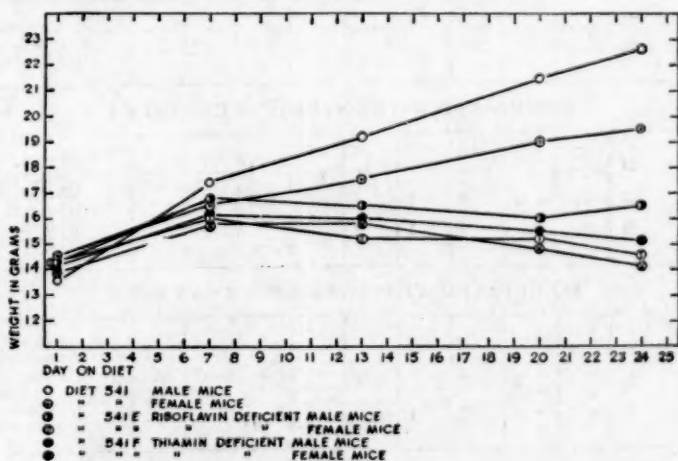


FIGURE 1.—Average rate of growth of mice fed on different diets.

respectively, had a weight curve parallel to those on 541 for 1 week, following this period their weight curve became stationary or showed a tendency to decline. Although the 0.5 microgram of riboflavin or thiamin chloride was sufficient to maintain life for the period observed, relative deficiency is indicated by the failure to gain weight on a parallel with the mice that received larger amounts of each of the two vitamins. The rate of growth is shown in figure 1.

*Experiment 1.*—Forty male and 40 female mice were fed as follows: 10 males and 10 females were fed ad lib. on diet 541; 15 males and 15 females received riboflavin deficient diet 541E; and 15 males and 15 females were given thiamin deficient diet 541F. Three weeks later 5 male and 5 female mice from each group were inoculated with pneumococcus type I by the intranasal route. In a like manner 5 males and 5 females were inoculated with pneumococcus type II. The remaining mice fed on diets 541E and 541F were inoculated in the

same manner with the sterile blood broth. The results are summarized in table 2 which shows that pneumococci of type I strain were less virulent for mice in each group and that more deaths occurred in the mice on the deficient diets inoculated with either type I or type II. The type I strain was used in the remainder of the experiments. The virulence was maintained by frequent passage of the seed organism through mice by intraperitoneal inoculation and recovery from the heart blood.

TABLE 2.—Results of experiment 1

INOCULATED WITH STERILE BLOOD BROTH												
Diet	Days on diet before inoculation	Day of death following inoculation										Remarks
		1	2	3	4	5	6	7	8	9	10	
541E.....	21	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	All 10 survived. 1 died. 9 survived.
541F.....	21	-----	-----	-----	-----	-----	1	-----	-----	-----	-----	
INOCULATED WITH PNEUMOCOCCUS TYPE I												
541.....	21	-----	-----	-----	-----	-----	-----	1	-----	-----	-----	1 died. 9 survived.
541E.....	21	-----	-----	3	1	-----	1	-----	-----	-----	-----	5 died. 5 survived.
541F.....	21	-----	-----	2	1	2	2	-----	-----	-----	-----	7 died. 3 survived.
INOCULATED WITH PNEUMOCOCCUS TYPE II												
541.....	21	1	-----	3	1	-----	-----	-----	-----	-----	-----	5 died. 5 survived.
541E.....	21	3	2	2	-----	1	-----	-----	-----	-----	-----	8 died. 2 survived.
541F.....	21	1	5	3	1	-----	-----	-----	-----	-----	-----	10 died. None survived.

*Experiment 2.*—Three groups of 100 mice each were fed diet 541, riboflavin deficient diet 541E, and thiamin deficient diet 541F, respectively. During the conditioning period before inoculation 2 mice from the first group, 3 from the second, and 1 from the third group died. After 21 days on the diet, 50 mice from each group were inoculated with pneumococci type I and the remainder were inoculated with sterile blood broth by the intranasal route. During the next 10 days 18 of the 50 inoculated mice on diet 541, 35 of those on diet 541E, and 37 on diet 541F died. Of the controls none of 48 on 541, 1 of 47 on 541E, and 7 of 49 on 541F died. Thus more of the inoculated mice died and death occurred earlier in mice on both the thiamin and riboflavin deficient diets than in the mice on diet 541. The results are summarized in table 3.

TABLE 3.—Results of experiment 2  
INOCULATED WITH PNEUMOCOCCUS TYPE 1

Diet	Days on diet before inoculation	Day of death following inoculation										Remarks
		1	2	3	4	5	6	7	8	9	10	
541.....	21	-----	-----	1	1	-----	6	8	2	-----	-----	18 died. 32 survived.
541E.....	21	-----	1	14	8	8	2	1	-----	-----	1	35 died. 15 survived.
541F.....	21	2	4	11	7	6	4	3	-----	-----	-----	37 died. 13 survived.
INOCULATED WITH STERILE BLOOD BROTH												
541.....	21	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	None died. 48 survived.
541E.....	21	-----	-----	-----	-----	1	-----	-----	-----	-----	-----	1 died. 46 survived.
541F.....	21	2	-----	-----	-----	1	2	1	1	-----	-----	7 died. 42 survived.

*Experiment 3.*—Three groups of 100 mice each were placed on diet 541, riboflavin deficient diet 541E, and thiamin deficient diet 541F, respectively. Half of each group was inoculated after 14 days on the diet. In this test the pneumococci appeared to be less virulent than in the previous test, as shown by only 8 deaths among the 50 mice on diet 541, as compared with 18 deaths among those on the same diet in the previous test. It will be noted, however, that there were more deaths, and that deaths occurred earlier, among the mice on both deficient diets than among those on diet 541. The results are summarized in table 4.

TABLE 4.—Results of experiment 3  
INOCULATED WITH PNEUMOCOCCUS TYPE 1

Diet	Days on diet before inoculation	Day of death following inoculation										Remarks
		1	2	3	4	5	6	7	8	9	10	
541.....	14	-----	-----	2	2	2	-----	-----	2	-----	-----	8 died. 42 survived.
541E.....	14	-----	-----	3	2	7	3	-----	-----	-----	-----	15 died. 35 survived.
541F.....	14	-----	-----	4	4	2	1	2	-----	-----	-----	13 died. 37 survived.
INOCULATED WITH STERILE BLOOD BROTH												
541.....	14	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	50 survived. 1 died.
541E.....	14	-----	-----	-----	-----	-----	-----	-----	-----	1	-----	49 survived. 1 died.
541F.....	14	-----	-----	-----	-----	-----	-----	-----	-----	1	-----	49 survived.

*Experiment 4.*—Two groups of 30 mice each were placed on diet 541 and 6 groups of 30 mice were fed riboflavin deficient diet 541E.



After 14 days one group of mice on 541 and three of the groups on riboflavin deficient diet 541E were inoculated with pneumococcus type I, as test groups. The remaining mice were similarly inoculated with sterile blood broth as control groups. Beginning on the day of inoculation 30 of the test mice and 30 of the control mice that were being fed riboflavin deficient diet 541E were given daily 100 micrograms of sodium riboflavin<sup>3</sup> in 0.2 ml. distilled water by subcutaneous injections and 30 test mice and 30 controls on the same diet were offered 100 micrograms of sodium riboflavin in 0.2 ml. distilled water in supplement cups. Among the inoculated mice in this test, 11 of 30 mice on diet 541 died while 17 of the 30 on riboflavin deficient diet 541E died. Seventeen of the 30 on riboflavin deficient diet 541E that received sodium riboflavin subcutaneously and 18 of 30 that received it in supplement cups died. No deaths occurred among the controls. The results are summarized in table 5.

TABLE 5.—Results of experiment 4  
INOCULATED WITH PNEUMOCOCCUS TYPE I

Diet	Days on diet before inoculation	Supplement	Day of death following inoculation										Remarks
			1	2	3	4	5	6	7	8	9	10	
541	14	None				4	4	2		1			11 died. 19 survived.
541E	14	None			6	5	2	2	1	1			17 died. 13 survived.
541E	14	100 micrograms sodium riboflavin subcutaneously.		1		2	8	4	1	1			17 died. 13 survived.
541E	14	100 micrograms sodium riboflavin orally.				5	4	4	2	3			18 died. 12 survived.
INOCULATED WITH STERILE BLOOD BROTH													
541	14	None											30 survived.
541E	14	None											Do.
541E	14	100 micrograms sodium riboflavin subcutaneously.											Do.
541E	14	100 micrograms sodium riboflavin orally.											Do.

The average weight curves of the control mice showed that the mice on diet 541 continued to grow throughout the period of the test, whereas all mice on riboflavin deficient diet 541E lost weight during the second week on the diet. After the supplements of sodium riboflavin were begun both groups gained weight. The weight of those on riboflavin deficient diet 541E that received no supplement of riboflavin was practically unchanged. Weight curves are given in figure 2.

*Experiment 5.*—This experiment was similar to experiment 4 except that thiamin deficient diet 541F was used instead of riboflavin deficient

<sup>3</sup> Sodium riboflavin is a water-soluble riboflavin preparation.

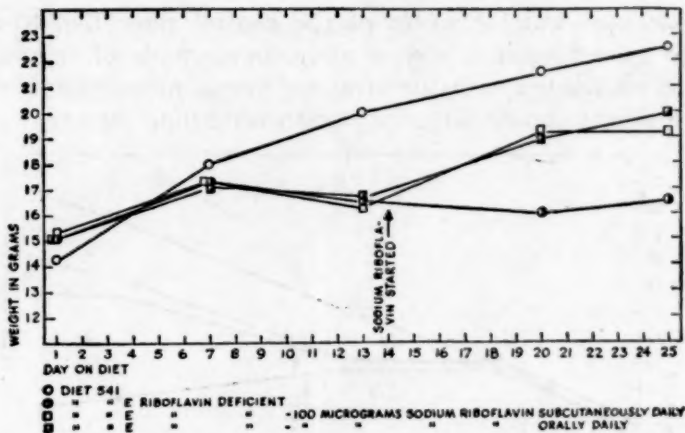


FIGURE 2.—Average rate of growth of male mice in experiment 4.

diet 541E. Groups of 30 mice were used and 200 micrograms of thiamin chloride were given subcutaneously and orally instead of sodium riboflavin. The mice that received the thiamin in the supplement cups took the supplement irregularly and the amount consumed was not determined.

Five of the 30 mice on diet 541 died; 9 of the 30 mice on the thiamin deficient diet 541F, 14 of the 30 on thiamin deficient diet 541F that received thiamin subcutaneously, and 8 of 30 that were offered it in supplement cups died. No deaths occurred among the controls. The results are summarized in table 6.

TABLE 6.—Results of experiment 5  
INOCULATED WITH PNEUMOCOCCUS TYPE I

Diet	Days on diet before inoculation	Supplement	Day of death following inoculation										Remarks
			1	2	3	4	5	6	7	8	9	10	
541	14	None		1	2	1		1					5 died. 25 survived.
541F	14	None		3	3	2		1					9 died. 21 survived.
541F	14	200 micrograms of thiamin chloride subcutaneously daily.		3	3		1	3	2	1	1		14 died. 16 survived.
541F	14	200 micrograms of thiamin chloride orally daily.			3			3	2				8 died. 22 survived.
INOCULATED WITH STERILE BLOOD BROTH													
541	14	None											30 survived.
541F	14	None											Do.
541F	14	200 micrograms of thiamin chloride subcutaneously daily.											Do.
541F	14	200 micrograms of thiamin chloride orally daily.											Do.

The average weight curves of the control mice (fig. 3) on the thiamin deficient diet increased after supplements of thiamin were begun as contrasted with the steady decrease in weight of the mice on the deficient diet that received no thiamin supplement.

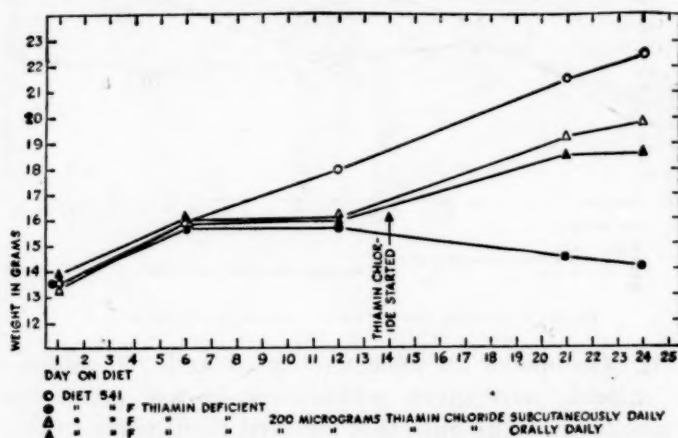


FIGURE 3.—Average rate of growth of male mice in experiment 5.

*Summary of experiments 1 to 5.*—In the experiments with riboflavin deficiency a total of 140 mice were fed diet 541 and the same number were fed riboflavin deficient diet 541E. Thirty-eight deaths occurred among the 140 mice fed on diet 541. Three deaths occurred by the third day, 10 by the fourth, and 16, or 42 percent, by the fifth day. Of the 72 deaths among the 140 mice fed on riboflavin deficient diet 541E, 27 occurred by the third, 43 by the fourth, and 61, or 84.7 percent of the total deaths, by the fifth day after inoculation with pneumococci. The results are summarized in figure 4.

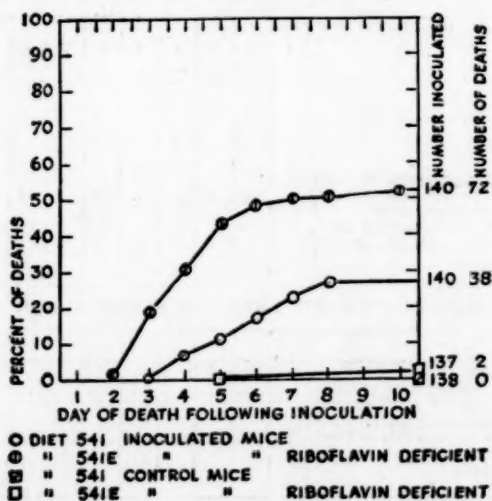


FIGURE 4.—Summary of results with diets 541 and 541E in experiments 1, 2, 3, and 4.



In the experiments with thiamin deficiency a total of 140 mice were fed diet 541 and the same number were fed thiamin deficient diet 541F. Of 32 deaths among the 140 mice fed on diet 541, 6 occurred by the third, 10 by the fourth, and 12, or 37.5 percent, by the fifth day after inoculation with pneumococci. Of the 65 deaths among the 140 mice on thiamin deficient diet 541F, 28 occurred by the third, 42 by the fourth, and 52, or 80 percent, by the fifth day after inoculation with pneumococci. The results are summarized in figure 5.

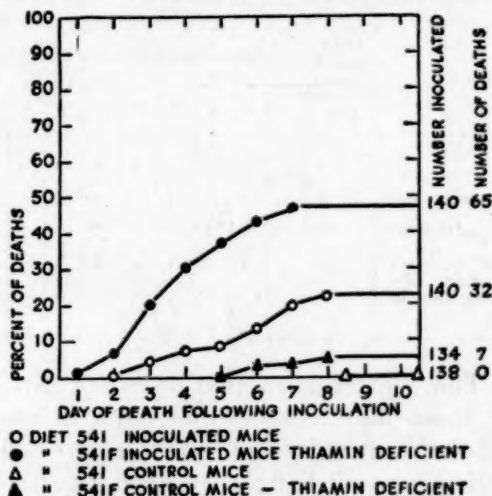


FIGURE 5.—Summary of results with diets 541 and 541F in experiments 1, 2, 3, and 5.

The above experiments do not prove a direct relationship to the specific deficiency since there is no data on the total quantity of food eaten by the experimental animals. Therefore, additional experiments were undertaken in order to determine whether the greater number of deaths among mice on the riboflavin deficient diets was related directly to riboflavin deficiency or to the quantity of food eaten.

*Experiment 6.*—Four groups of 30 mice each were fed ad lib. Two groups received the control diet 597A and two groups the riboflavin deficient diet 597E, both of the latter being given 200 micrograms of sodium riboflavin daily by subcutaneous injection beginning at the time of inoculation. Four additional groups of 30 mice each were fed equal amounts of diet, two of them receiving the control diet and the remaining two the riboflavin deficient diet. The amount of food allowed these four groups was limited by the quantity eaten daily by the mice on the riboflavin deficient diet. Fifteen days after the beginning of the experiment the mice in one of the groups fed by each of the various methods were inoculated with pneumococci type I, by the intranasal route, and the other groups were inoculated in a similar manner with sterile blood broth as controls.

The smallest number of deaths occurred in each of the two groups that were fed on the control diet 597A. The greatest number of deaths occurred in the group that received the riboflavin deficient diet that was supplemented with 200 micrograms of riboflavin daily by subcutaneous injections beginning at the time of inoculation. The results are summarized in table 7. No deaths occurred among

TABLE 7.—Results of experiment 6  
INOCULATED WITH PNEUMOCOCCUS TYPE I

Diet	How fed	Days on diet before inoculation	Day of death following inoculation										Remarks
			1	2	3	4	5	6	7	8	9	10	
597A	Ad lib.	15		1		1	1	4	3	2	1	1	(14 died, 16 survived.
597E	Ad lib. amounts eaten recorded.	15		1		4	5	4	2	1			(17 died, 13 survived.
597A	Amounts equal to 597E.	15			1		3	7		2			(13 died, 17 survived.
597E	Ad lib. plus 200 micrograms sodium riboflavin daily after inoculation.	15		1	2	1	5	5	5	1	1		(21 died, 9 survived.

the controls. The control mice that were fed riboflavin deficient diet 597E and those that received diet 597A in amounts equal to the average amounts eaten by the former group had weight curves that were practically parallel (fig. 6). Each group lost weight after

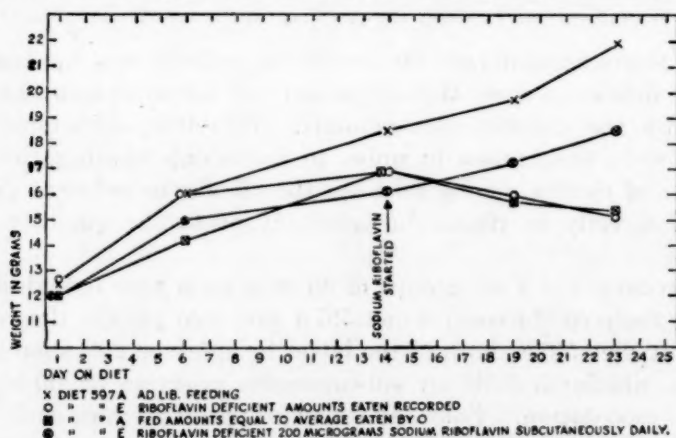


FIGURE 6.—Average rate of growth of male mice in experiment 6.

the second week, whereas the group fed ad lib. on diet 597A continued to show increased weight throughout the period of observation. The group that received riboflavin deficient diet 597E that was supplemented with 200 micrograms of sodium riboflavin daily by subcutaneous injection after 15 days on the diet gained weight throughout the remainder of the period of observation.

## PAIRED FEEDING EXPERIMENTS WITH LITTER MATES

Litters of 4 mice of the same sex of approximately equal weight, taken at weaning, were placed in individual one-quarter inch wire mesh cages without bedding so that the diet wasted could be determined and so that the mouse could not have ready access to its feces and urine. Two of the mice were fed diet 597AX and the other two riboflavin deficient diet 597EX. These diets contained twice the amounts of vitamins incorporated in diets 597A and 597E, to prevent multiple vitamin deficiencies when small amounts of food were eaten, except that diet 597EX contained only 0.5 microgram of riboflavin per gram. Each mouse in the litter received the exact amount of diet eaten by the mouse that ate the least during the previous 24 hours. The mouse with the poorest appetite received an excess amount of diet each day. This procedure was followed throughout the period of observation.

After a period of about 2 weeks on the diets, 1 mouse from each litter on each of the two diets was inoculated with pneumococci type I, and the controls with sterile blood broth in the manner previously described. All mice were observed for a period of 10 days. Deaths were recorded and cultures were made in beef infusion broth from the heart blood of the mice dying during this period. Pneumococci were recovered from all of the inoculated mice by this procedure, whereas cultures from the blood of each of the control mice studied remained sterile.

*Experiment 7.*—Eight litters of male mice and six litters of females were used. Inoculations were made after 14 days on the diet. Following the death of one of the mice of a given litter in this study the litter mates were fed ad lib. There were 3 deaths (1 male and 2 females) in the infected litters on diet 597AX before any of their litter mates. There were 9 deaths (5 males and 4 females) among the infected mice on riboflavin deficient diet 597EX before their corresponding mates. One death occurred among the controls that were fed on diet 597AX before any of the litter mates. A total of 11 of 14 infected mice on riboflavin deficient diet 597EX died during the 10-day observation period. Only 5 infected mice on diet 597AX died during the same time. Two controls on 597AX and 1 on riboflavin deficient diet 597EX died during the period of observation. The results are summarized in table 8.

*Experiment 8.*—This study was similar to experiment 7. Eight litters of 4 males and nine litters of 4 females were pair fed. Inoculations were made after the mice had been fed for 15 days on the respective diets. Three mice (2 males and 1 female) on diet 597AX died and the litter mates on riboflavin deficient diet 597EX were discarded while 7 (4 males and 3 females) on riboflavin deficient diet 597EX died and their respective litter mates on diet 597AX were discarded. In

four instances the litter mates in the inoculated groups were found dead within a short period of each other (within 3 hours or less). No deaths occurred among the control groups earlier than their inoculated mates.

TABLE 8.—*Total number of deaths in paired feeding of litter mates in experiment 7*  
INOCULATED WITH PNEUMOCOCCUS TYPE I

Diet	Day on diet before inoculation	Day of death after inoculation										Remarks
		1	2	3	4	5	6	7	8	9	10	
597 AX	14			1	1		1	1	1			{5 died. 9 survived.
597 EX	14		1	1		3	2	2	1		1	{11 died. 3 survived.
INOCULATED WITH STERILE BLOOD BROTH												
597 AX	14					1				1		{2 died. 12 survived.
597 EX	14								1			{1 died. 13 survived.

The results of experiments 7 and 8 indicate that the higher fatality rate in the mice on the riboflavin deficient diets is not due to restricted total food intake.

#### SUMMARY

It is shown that mice that have been fed diets containing less than minimum requirements of riboflavin or thiamin for normal growth are more susceptible to a fatal infection with pneumococcus type I, when inoculated by the intranasal route, than are mice that have received a diet containing an amount of these vitamins sufficient for good growth. That the increased susceptibility to fatal pneumococcus infection among the mice fed on the riboflavin deficient diets is not due to malnutrition following anorexia was demonstrated in the paired feeding experiments. One experiment showed that there were more deaths in a group of mice on the riboflavin deficient diet when the total food intake was equal to that of a group on a similar diet which contained enough riboflavin for good growth. Also by two paired feeding experiments with litter mates it was again shown that there were more deaths among the mice on the riboflavin deficient diet than in the mice on the good diet during the period of observation.

It was observed that the administration of 100 micrograms of sodium riboflavin daily, beginning at the time of inoculation with pneumococcus type I, to mice that had been fed a diet deficient in this vitamin did not reduce the mortality. When 200 micrograms of sodium riboflavin were administered to 30 riboflavin deficient mice, or 200 micrograms of thiamin hydrochloride to 30 thiamin deficient mice, by subcutaneous injection daily, beginning at the time of inoculation

with pneumococci, the number of deaths was greater than was shown among the respective riboflavin or thiamin deficient infected animals. The number is too small to be significant but the observation is sufficiently interesting to warrant further experimentation.

#### CONCLUSIONS

1. Under the conditions of these experiments mice deficient in riboflavin or thiamin were more susceptible to a fatal infection with pneumococcus type I when inoculated by the intranasal route than were mice fed on a diet containing enough of these vitamins for good growth.

2. Paired feeding experiments indicate that this effect in the mice on the riboflavin deficient diet is not due to a restricted total food intake.

3. The daily administration of riboflavin or thiamin in amounts 5 to 10 times that in the control diet, to the mice on diets deficient in these substances, respectively, at the time of inoculation with pneumococcus type I, did not reduce the number of animals dying from the infection.

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### ON THE ROLE OF PARASITE PIGMENT IN THE MALARIA PAROXYSM<sup>1</sup>

By DEMPSIE B. MORRISON and W. A. D. ANDERSON

In the course of studies<sup>2</sup> of bile pigment metabolism in dogs following injections of disodium ferrihemate (alkali hematin), attention was drawn to certain similarities between the induced clinical and pathological picture and the symptoms and tissue pathology in malaria. Ferrihemate is exceedingly toxic to dogs, readily causing death in convulsive shock. However, purified ferrihemate may be given repeatedly intravenously, slowly and in controlled amounts, with resultant milder symptoms of toxicity and survival of the animal. In dogs

<sup>1</sup> From the Departments of Chemistry and Pathology, University of Tennessee College of Medicine, Memphis. Received for publication July 23, 1941.

<sup>2</sup> To be published.



killed by ferriheme administration or sacrificed after long-continued ferriheme administration, widespread deposition of pigment in the reticulo-endothelial system and extensive plugging of capillaries by pigment or pigment-containing masses resemble strikingly pathological findings in fatal human malaria.

That a causal relationship may exist between pigment liberated by sporulating parasites and the malaria paroxysm has been suggested by others. Brown (1) was led to this conclusion by observations of rabbits injected with ferriheme solutions. Among symptoms noted were shivering, reduction in surface temperature, and elevation in rectal temperature. Brown's solutions were prepared by dissolving heme crystals, obtained directly from blood by the Schalejew method (2), in solutions containing 0.85 percent NaCl and 1.5 to 2.0 percent  $\text{NaHCO}_3$ , and were not of uniform composition. Brown stated, "With different preparations of heme \* \* \* variations in solubility are continually appearing \* \* \*. Reference is made to this feature of the heme solution to indicate the difficulty in maintaining absolutely uniform experimental conditions and accurate dosage." Duesberg (3) reports that, whereas in man intravenous injection of ferriheme solutions prepared from once-crystallized heme (Schalejew method) caused chills and fever, malaria-like symptoms were not observed when recrystallized heme was used. Bearing also upon the possibility that Brown's findings were determined by nonferriheme contaminants is Barron's (4) observation that reproducible oxidation-reduction potentials can be obtained for solutions of ferriheme only when the latter is prepared from recrystallized heme.

Fairley and Bromfield (5) have described a brown extracorporeal pigment in the plasma of a case of blackwater fever. Since spectroscopic tests indicated a similarity to but not identity with methemoglobin, the pigment was named pseudomethemoglobin. Further study indicated that the pigment was a compound of ferriheme and plasma albumin, and Fairley (6) proposed for this compound the name "methemalbumin." Fairley (7) now claims, on the basis of the nonspecific Schumm (8) test, that ferriheme may exist in the circulating plasma only in combination with albumin and never in the free state.

Since fever was not a symptom of ferriheme toxicity in our dogs we have undertaken to extend our observations upon a species of animal (monkey) in which, unlike the dog, experimental malaria may be readily induced by a plasmodium whose intracellular pigment has been identified as ferriheme (9).

#### EXPERIMENTAL PROCEDURE AND METHODS

*Macacus rhesus* monkeys were used throughout. Five monkeys received ferriheme injections; 16 monkeys were infected with

*Plasmodium knowlesi* (Rockefeller strain<sup>3</sup>); and some 20 normal monkeys served as controls.

The excessive virulence of the original strain of *P. knowlesi* was reduced temporarily by passage through man, and the attenuated strain was used in some animals.

The course of infection was followed in blood smears taken from the tail. The degree of infection was recorded as the percentage of total erythrocytes infected with parasites; in terminal stages this was sometimes as high as 76 percent. Segmentation occurred at approximately 24-hour intervals. By examination of blood films, it was possible from the smears to predict with considerable accuracy when segmentation would occur.

Since we were primarily interested in pigment metabolism, the animals were usually sacrificed when the extent of parasitization was such as to predict early death, and near the time of segmentation when pigment would be present in largest amount. The animals were bled under nembutal anesthesia by cannulation of the femoral artery or, when the animal had collapsed and died or was dying, blood was taken by syringe from the heart. Solid potassium oxalate was used as anticoagulant, and analyses were made as promptly as possible.

*Ferrihemate injections.*—Disodium ferrihemate (10) was prepared by equilibrating an excess of recrystallized hemin with standard NaOH solution. After removal of excess hemin by centrifugation, the saturated ferrihemate solution was diluted with sterile 0.9 percent NaCl to give a final concentration of 160 mg. of ferrihemate per 100 cc. Solutions thus prepared had a pH of approximately 7.6, and were stable and sterile.<sup>4</sup>

The ferrihemate solutions, at a temperature of 28°–30° C., were injected into the saphenous vein at a rate of 0.5 to 1.0 cc. per minute. The amount of ferrihemate given as the disodium salt in a single injection varied from 5.0 to 20.6 mg. per kilo of body weight. The number of injections given to each of the 5 monkeys, the total amounts of ferrihemate administered, time intervals between injections, and other related data are shown in table 1.

*Blood analyses.*—Blood samples were centrifuged in graduated tubes. After the volumes of cells and plasma were noted, the plasma was removed and reserved. The packed cells were diluted either with 0.9 percent NaCl to original sample volume (method A) or with distilled water to some appropriate volume (method B).

<sup>3</sup> Kindly supplied by Dr. L. T. Coggeshall of the International Health Division of the Rockefeller Foundation Laboratories in the Rockefeller Institute for Medical Research.

<sup>4</sup> We are indebted to Dr. A. D. Dulaney, of the Division of Pathology and Bacteriology, for tests of sterility.

TABLE 1.

Animal No.	Weight, kilos	Date of injection	Ferrihemate, mg. per kilo	Remarks
H-2-----	4.8	1940 Jan. 26	5.0	Control injection of 0.9 percent NaCl.
		Feb. 6	8.35	
	4.5	Feb. 18	None	
	4.5	Feb. 21	12.4	
	4.5	Mar. 13	14.2	
	4.5	Mar. 14	None	Ferrihemate in blood.
H-4-----	4.5	Apr. 1	None	Killed and autopsied.
	3.6	Feb. 14	17.8	
	3.2	Mar. 14	15.0	
	3.2	Apr. 1	None	Killed and autopsied.
H-7-----	3.4	Jan. 25	None	Control injection 0.9 percent NaCl.
	3.4	Feb. 26	18.8	Died 23 minutes after injection.
H-8-----	3.1	Jan. 29	20.6	Died 30 minutes after injection.
H2-8-----	3.6	Feb. 13	11.1	
	3.6	Feb. 26	17.8	
	3.6	Mar. 11	None	Killed and autopsied.

All spectrographic quantitative analyses of pigments were made with the Bausch & Lomb universal spectrophotometer, with an assembly of cups which permitted readings with the following depths of solutions: 1, 2.5, 5, 10, 20, 50, and 100 mm. When the spectral region to be covered extends from 500  $m\mu$  to 700  $m\mu$ , as in the present work, the depth of solution must be varied for different wave lengths. Thus, if a solution of hemoglobin is diluted to give optimal readings in the region of maximal absorption (500  $m\mu$  to 590  $m\mu$ ) in a 10 mm. cup, absorption from 600  $m\mu$  to 700  $m\mu$  is too small for accurate readings. If the same solution is placed in a longer cup, readings in the red are greatly improved. This consideration is of the utmost importance in searching for small amounts of pigment which absorb in the red (methemoglobin, methemalbumin, etc.) which may be mixed with relatively large amounts of oxyhemoglobin.

To simplify the spectrophotometric data all such curves, except H-7-A, figure 1, are calculated for a cup of unit length 1 cm. and for the undiluted blood or urine.

1. Plasma pigments: All plasmas were analyzed spectrophotometrically through the range 500-660  $m\mu$ ; in some instances the spectral range was extended to 700  $m\mu$ . In addition, the plasmas were inspected with a Zeiss direct vision spectroscope for qualitative detection of methemoglobin, methemalbumin, or ferrihemate. Occasional tests for bilirubin were made by the Gibson and Goodrich (11) modification of the Van den Bergh method.

2. Parasite pigment: Dilution of packed cells with distilled water (method B) lyses the cells and releases the parasites. The latter swell but do not disintegrate in distilled water. The parasite mass was thrown down and washed repeatedly on the centrifuge with distilled water until hemoglobin or other soluble pigment could no longer be detected by the spectroscope in the wash water.

The pigment of *Plasmodium knowlesi* exists in the parasite as pre-formed ferriheme (9). Its quantitative determination was done spectrophotometrically on acid-acetone extracts of the washed parasites.<sup>5</sup> Readings may be made at any wavelength but, since the absorption curve shows maxima at 540  $m\mu$  and 640  $m\mu$ , we have employed the latter band.

Calculations are based upon the following experimentally determined equivalents: An oxyhemoglobin solution equivalent in concentration to 1 millimol per liter of ferrihemic acid and having an oxygen capacity of 1 millimol (22.4 ml.) at S. T. P., when converted to the cyanmethemoglobin derivative and read in a cup of 1 cm. length is characterized by an extinction coefficient of 11.5 at 540  $m\mu$ ; when the oxyhemoglobin is converted by acid-acetone to ferrihemic acid in equivalent concentration, and read in a cup of 1 cm. length, the extinction coefficient is 5.11 at 640  $m\mu$ .

3. Intracellular pigments: Aliquots of suspended cells (method A) or laked cells (method B) were analyzed for total pigment as ferrihemic acid by the acid-acetone method. One volume of cells or blood is added to approximately 23 or 45 volumes of acetone which contains 2 percent by volume of concentrated HCl, and the mixtures are then made up with the acid-acetone to 25 or 50 volumes depending on the pigment values. Globin is precipitated while the heme is converted to ferrihemic acid and remains in solution. The globin is removed by centrifugation in tightly corked tubes, and pigment is determined in the supernatant solution.

The soluble pigments (method B), after the parasites had been removed by centrifugation, were determined spectrophotometrically on aliquots prepared as follows: (a) Without further treatment, in which case pigments would be present presumably unaltered; (b) after addition of NaF or NaCN for their effect upon absorption by methemoglobin; (c) after converting all hemoglobin to cyanmethemoglobin. Comparison of the absorption curves should determine the presence or absence of methemoglobin or soluble ferriheme. In addition, the several solutions were examined qualitatively with the Zeiss spectroscope for faint bands.

Aliquots of cell suspensions obtained from normal control animals were analyzed for hemoglobin by the oxygen capacity method (13), by the spectrophotometric-cyanmethemoglobin method (14), and by the acid-acetone method. Since it is valid to assume that hemoglobin is the only pigment of normal erythrocytes, these determinations served to establish the equivalents employed in calculating pigment concentration from observed extinction coefficients of acid-acetone solutions of ferrihemic acid.

<sup>5</sup> This method is adapted from a procedure used by one of us in a study of the influence of pH upon the dissociation of hemoglobin (12).

Since, with the possible exception of animal M-10, the only *soluble* pigment present in detectable amounts in parasitized blood was hemoglobin, it is possible to calculate from total pigment and hemoglobin values the percentage of hemoglobin which had been converted to parasite pigment.

*Tissue analyses.*—Total pigment was determined in the spleen of one ferrihemate-injected monkey and in the spleens of two malarial monkeys. The tissues were ground with sand, extracted with acid-acetone, and the extract analysed spectrophotometrically in the usual manner.

*Urine analyses.*—Urines of malarial animals were examined for hemoglobin; when this was present it was determined spectrophotometrically. Upon the urines of all animals the following routine observations were made: Specific gravity, reaction to litmus, reducing sugars, proteins, bile pigments, urobilogen, and, occasionally, ether soluble porphyrins.

Although the animals were kept in individual steel metabolism cages, with wire mesh bottoms above stainless steel collecting pans, accurate collection of urines was complicated by the animals' habit of throwing water with their hands from the drinking cups.

## RESULTS

### FERRIHEMATE-INJECTED MONKEYS

*Symptoms.*—Injection of ferrihemate in unanesthetized monkeys at first stimulates respiration and heart rate slightly. Surface capillaries contract; face, ears, axilla, groins, gums, and tongue blanch; later, these regions may become slightly cyanotic. As more ferrihemate is given, the face and ears especially and the nose become tan in color, the animal licks his lips, and frequently vomit contractions appear. Respiration may become labored and abdominal in type. Lacrimation and salivation may occur. Rectal temperature may rise or fall. Some animals exhibit a very marked nystagmus.

With the higher dosage, symptoms of weakness and shock appear. If the injection is stopped and the animal returned to its cage signs of vertigo, weakness, and lassitude are manifest for some time. Usually recovery appears to be complete within 1 or 2 hours, although in one animal a very pronounced edema around the eyes persisted for 24 hours.

Two animals which received the larger dosages of ferrihemate, after the usual preliminary symptoms, rapidly became convulsive, collapsed, and died a few minutes later. Although respiration had ceased, the heart, on exposure, was found to be still beating. In monkey H-7, the heart, while fibrillating, still had a slow and relatively strong beat. Visceral organs were congested with blood.



*Blood picture.*—In figure 1, curves H-7 and H-8 describe the pigment in the plasmas of 2 monkeys which were killed by ferrihemate injections. A slight hemolysis in monkey H-7 is revealed by peaks at  $540\text{ m}\mu$  and  $577\text{ m}\mu$ . When these curves are compared with those representing plasmas of malaria-infected monkeys (fig. 2), it is evident that no appreciable amount of soluble pigment is found in the plasma of parasitized blood.

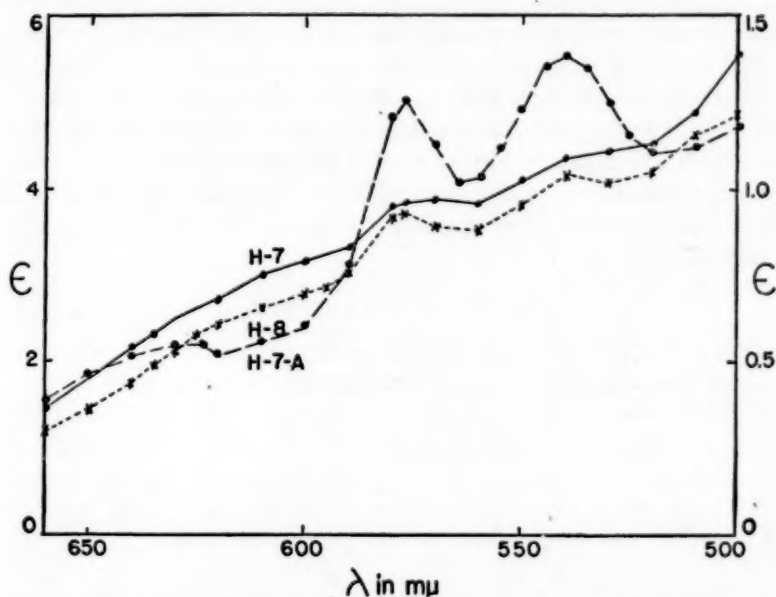


FIGURE 1.—Spectrophotometric curves of plasmas of monkeys H-7 and H-8 injected with disodium ferrihemate. Curve H-7-A is that of a pigment which may be methemalbumin. Read curves H-7 and H-8 against scale to the left and curve H-7-A to the right.

Curve H-7-A, figure 1, is that of a sparingly soluble pigment obtained after removal of plasma from a sample of blood of monkey H-7 and laking the cells with distilled water. After centrifuging and decanting the hemoglobin solution, a small amount of brownish residue was ground in distilled water to give a suspension which was again centrifuged. Thus was obtained an apparent solution or colloidal dispersion upon which curve H-7-A was determined. Since this curve exhibits a peak at approximately  $625\text{ m}\mu$ , it may represent Fairley's (6) methemalbumin contaminated with oxyhemoglobin.

Animal H-2 was injected with 14.2 mg. of disodium ferrihemate per kilo of body weight in the afternoon and a sample of blood was taken the following morning. When this blood was centrifuged, a thin band of greyish color collected between the red and white cell layers. This band had the appearance of a layer of parasitized erythrocytes. Microscopic examination of a smear of the material of

the band demonstrated that it was composed mainly of leucocytes containing phagocytized pigment.

*Spleen.*—Monkey H-2-8 was injected on February 13 with 11.1 mg., and on February 26 with 17.8 mg., of ferrihemate per kilo of body weight. On March 11, the animal was killed and the spleen analyzed for total pigment. The relatively small weight of spleen and low concentration of pigment are to be compared (table 2) with the findings in malaria-infected monkeys.

*Other tissues.*—Microscopic findings at autopsy<sup>a</sup> of all ferrihemate-injected animals disclosed that the pigment had precipitated and occluded smaller vessels and capillaries. It is suggested that observed clinical symptoms are related, at least in part, to such occlusions which, when occurring in a vital location, cause death. In our experience with monkeys and a much larger series of dogs, if an animal survives an injection for approximately 30 to 45 minutes it will survive indefinitely.

#### MALARIA-INFECTED MONKEYS

*Symptoms.*—The general clinical picture develops as follows: Approximately 5 to 7 days after intramuscular inoculation of the animal with blood containing *Plasmodium knowlesi*, the first parasitized erythrocytes may be demonstrated in thick smear. Within the next 24 hours 6 to 8 percent of red cells are parasitized. As segmentation is repeated there is a progressive increase in the number of parasitized erythrocytes. In some animals the extent of parasitization of red cells has reached 76 percent. Hemoglobin falls rapidly and cell volume diminishes as the infection progresses. Near the terminal stage, anemia is so severe that blood for smear may be obtained from the tail only with difficulty.

Only in terminal stages, when anemia is very severe, is there significant curtailment of activity. Near or at the time of last segmentation symptoms of vertigo, uneven respiration, and elevated temperature (to 104.8° F.) are observed. The animals may walk unsteadily, but just before death they tend to lie on the abdomen with face in hands. If removed from the cage at this time, however, they still are capable of remarkable activity. Death comes suddenly with failure of respiration before the heart stops. In our series, death occurred, regardless of degree of infection, only when the cell volume had fallen to 10 percent or less and hemoglobin below 25 percent of normal.

In the several animals which were inoculated with *P. knowlesi* after human passage, the infection did not reach as high levels of parasitization as in animals receiving the nonattenuated strain. However, the characteristic anemia developed progressively, and the animals died

<sup>a</sup> A detailed report will be published of gross and microscopic findings at autopsy of ferrihemate-injected and malaria-infected animals.

about 6 days after initial appearance of parasites in the peripheral blood, as compared with 3 or 4 days for the more virulent strain.

*Blood picture.*—Figure 2 presents spectrophotometric analyses of plasmas of 4 normal and 6 malaria-infected monkeys. Curves 1, 2, and 3 represent infected monkeys M-4, M-9, and M-10, respectively, and demonstrate a very marked hemoglobinemia (as noted below, hemoglobinuria was also observed in these animals).

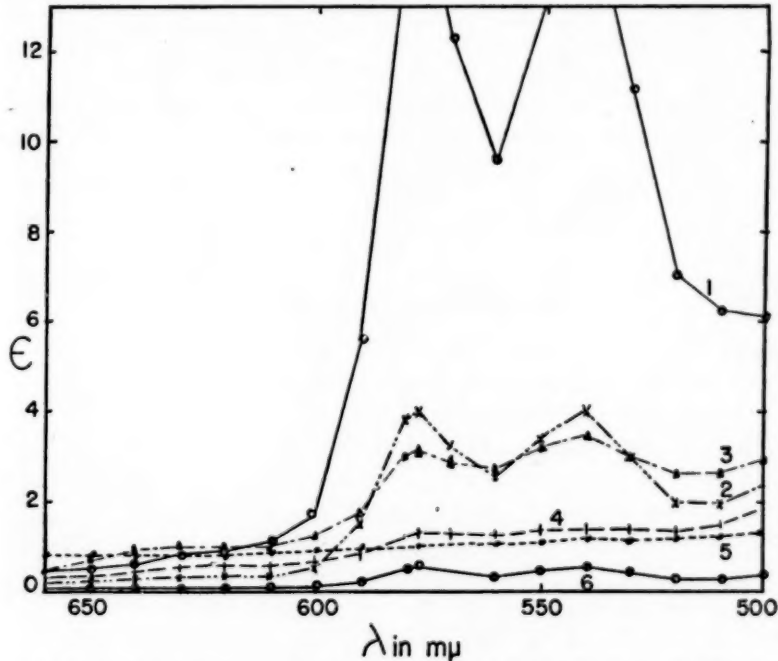


FIGURE 2.—Spectrophotometric curves of plasmas of normal and infected monkeys. Curves 1, 2, and 3 are of infected monkeys M-4, M-9, and M-10, respectively, and these animals showed a pronounced hemoglobinuria. Curve 4 is a composite of the curves of 3 infected animals which showed a slight hemoglobinemia and no hemoglobinuria. Curve 6 is the composite curve for 4 normal monkeys. Curve 5 describes a suspension of finely ground malarial parasites in distilled water.

It is to be emphasized that the optical clarity of plasmas from malaria-infected monkeys varies considerably, and may be correlated with the time of segmentation. If the blood sample is taken just before segmentation, when the parasites are largely mature but before rupture of the erythrocytes, the plasma has reasonably good optical quality. If segmentation has occurred and the plasma is loaded with very small parasite masses, satisfactory optical clarity cannot be obtained even with prolonged centrifuging.

We believe that turbidity, due to such semicolloidal parasite material, is responsible for absorption in the region of 630  $m\mu$  of curve 3 (monkey M-10), which is otherwise suggestive of methemoglobin. With the hand spectroscope no absorption at this wave length could be detected.

Curve 4 is a composite of individual analyses of plasmas of malarial animals M-1, M-6, and M-8. No appreciable hemoglobinemia is seen in these three cases. However, the plasmas had about the same turbidity as in animal M-10, and exhibit comparable absorption in the red.

Control curve 6 is the average of four plasmas obtained from normal animals with technique comparable to that employed in drawing blood from parasitized animals.

Curve 5 represents the supernatant centrifugate of a finely ground suspension of hemoglobin-free parasites in distilled water.

Comparison of spectrophotometric curves (fig. 3) of water soluble pigments present after removal of parasites from laked cell mixtures

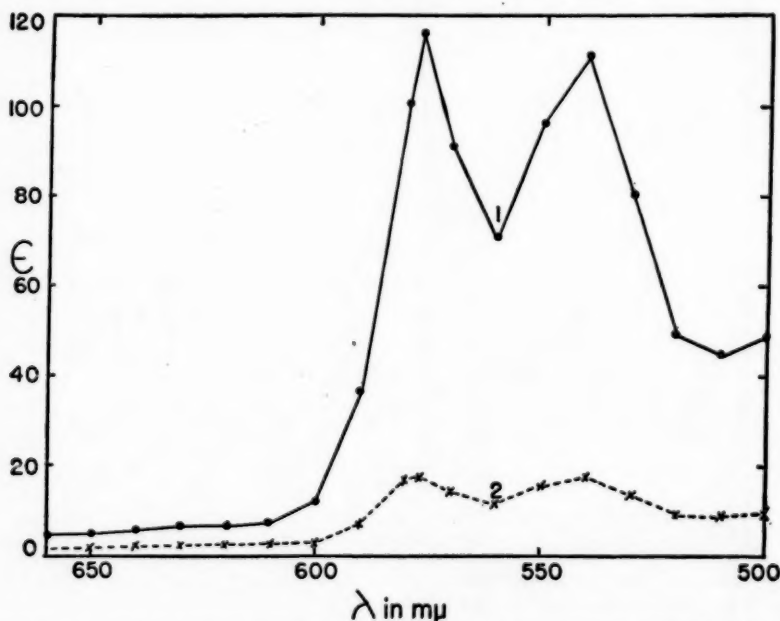


FIGURE 3.—Spectrophotometric curves of the soluble erythrocyte pigment (oxyhemoglobin) of 11 normal monkeys, curve 1, and of 6 malaria-infected animals, curve 2. The curves are calculated for a 1 cm. cup and for the undiluted blood.

(method B) indicates that the only soluble pigment was hemoglobin. Slight absorption in the red can again be accounted for by turbidity due to parasite material which could not be removed by centrifugation. Curve 1, figure 3, is the composite oxyhemoglobin curve for the 11 normal monkeys, and is to be contrasted with curve 2, the composite oxyhemoglobin curve for the six infected animals. Comparison of these two curves (cf., also, figs. 4 and 5) emphasizes the profound anemia which characterizes *P. knowlesi* infection in the monkey. It may be noted, in this connection, that no significant increases in plasma bilirubin could be detected in the six infected animals studied.

The relative amount of pigment circulating as parasite pigment in comparison to total pigment (hemoglobin-heme plus parasite ferrihemate), may vary from practically none to as much as 42 percent,

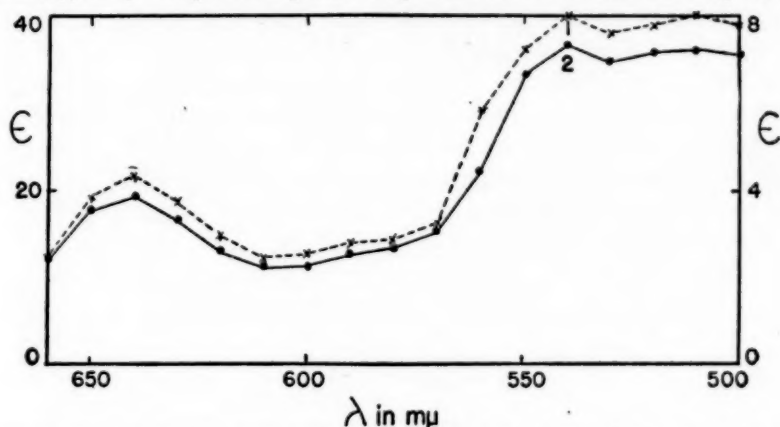


FIGURE 4.—Spectrophotometric curves for the total ferrihemate in acid-acetone obtained from hemoglobin and parasites (curve 2) of monkey M-4 and for the ferrihemate obtained from the hemoglobin free parasites (curve 1). Curves are calculated for a 1 cm. cup and for the undiluted blood. Read curve 2 against scale to the left and curve 1 against scale to right.

depending upon degree of parasitization and the stage of the parasite cycle. In figure 4, curve 2 represents the total pigment (as ferrihemate) of infected monkey M-4, and curve 1, the parasite pigment. From these curves it may be calculated that 22 percent of the total circulating pigment is parasite pigment.

In figure 5 are shown the progressive fall in hemoglobin and its relation to total circulating pigment in a heavily infected monkey

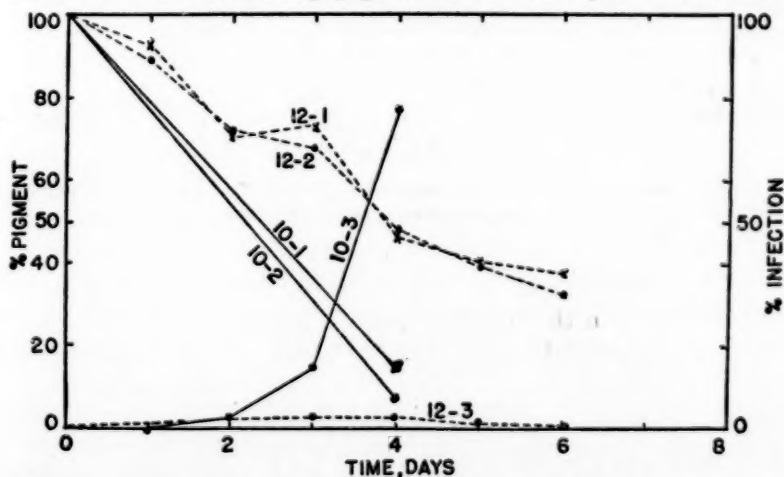


FIGURE 5.—Comparison of the total pigment and hemoglobins with degree of infection of animals M-10 and M-12. Curves 10-1 and 12-1 represent total ferrihemate expressed as percent of the normal for these animals. Curves 10-2 and 12-2 are the hemoglobin values in percent of the normal. Curves 10-3 and 12-3 are the percent of erythrocytes infected with parasites. Read curves 1 and 2 against the scale to the left and curve 3 to the right.

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(M-10), which survived for 4 days after parasites were first demonstrated in the blood, and a monkey (M-12) with milder infection which was sacrificed on the sixth day.

*Spleen.*—The data of table 2 illustrate the relatively large increase in size and weight of spleen (infected monkeys M-16 and M-18) when gorged with parasites, and the tremendous concentration of parasite pigment in this organ. Such spleens are under so much pressure that they tend to round up; when slit open in the long axis their contents bulge outward. They contain practically no hemoglobin, and what little fluid may be expressed resembles plasma more than whole blood.

TABLE 2.

Animal No.	Weight, kilos	Weight spleen, gm.	Ferrihemate, mg. per 100 gm. spleen
H2-8.....	3.4	5.5	47
M-16.....	2.0	15.0	495
M-18.....	2.5	21.0	526

*Urine picture.*—Collections were made of 237 specimens of urine from normal and malaria-infected monkeys. Of these, 174 samples were not contaminated with food and 61 percent were alkaline to litmus. In approximately 100 urines which were not contaminated and probably not diluted by water thrown from drinking cups, the specific gravity ranged from 1.005 to 1.032 with the majority between 1.010 and 1.022. Urobilinogen, bile pigment, and ether-soluble porphyrins varied from negative to traces and could not be related to the course or extent of infection. Reducing sugars were absent. Protein was found only at the terminal stage of infection in some animals and was always associated with and probably identical with hemoglobin.

In figure 6, curves M-9 and M-10 represent spectrophotometric analyses of undiluted urine specimens taken from the bladders of 2 of 3 malaria-infected monkeys which had exhibited pronounced hemoglobinuria. Since in the plasmas of these 2 monkeys it had not been possible to demonstrate a significant concentration of methemoglobin (fig. 2, curves 2 and 3), it is obvious that a considerable conversion of hemoglobin to methemoglobin has occurred during or after excretion. That such conversion occurs, particularly in acid urine, is well known. It may be noted that both urines here described were acid in reaction to litmus.

#### DISCUSSION

The essentially normal urine picture, with only occasional hemoglobinuria, in malaria-infected monkeys is to be credited, we believe, to the rapid course of infection with *P. knowlesi*. Erythrocytes are dehemoglobinized by the invading parasite and, at segmentation, the

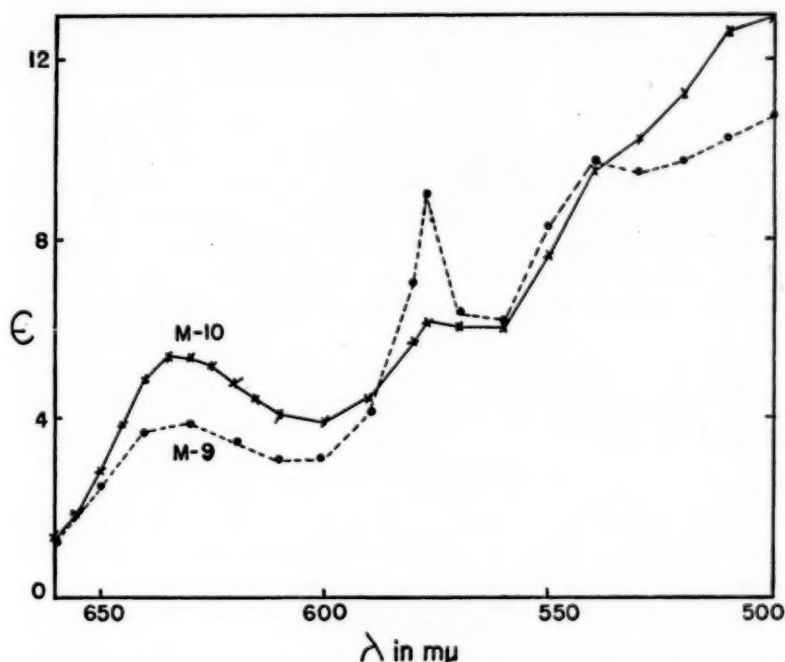


FIGURE 6.—Spectrophotometric curves of the undiluted bladder urines of infected animals M-9 and M-10. Calculated for the undiluted urine in a cup of 1 cm. Note the severe hemoglobinuria and methemoglobinuria.

end product of parasite pigment metabolism, ferrihemate, is enclosed within the parasite and not liberated in soluble form in significant amounts within the circulation. These pigment-loaded parasites are rapidly phagocytized by the reticulo-endothelial system.<sup>7</sup> Blocking and congestion of capillaries with parasites may well be imagined to cause intravascular damage and hemorrhage and thus account for hemoglobinemia and hemoglobinuria.

Since hemoglobin is a renal threshold substance, hemoglobinuria following a paroxysm is determined by the degree of hemoglobinemia. Thus, in figure 1, curves 1, 2, and 3 represent animals which exhibited definite hemoglobinuria coincident with the significant hemoglobinemia, whereas the 3 animals represented in composite curve 4 did not have hemoglobin in the urine at the lower level of hemoglobinemia indicated.

In view of our findings with ferrihemate-injected monkeys and dogs, and the observations of Brown (1) we have been somewhat surprised to find little, if any, ferrihemate in soluble form in the circulation of malaria-infected monkeys. We can discover in our present work no evidence of causal relationship between symptoms of malaria toxicity and parasite pigment *per se*. In our animals, toxic manifestations

<sup>7</sup> See footnote 6.

appeared only when a severe anemia had developed and the reticulo-endothelial system had been overwhelmed by accumulation of parasites.

## SUMMARY

1. There are important differences between the symptoms of ferrihemate intoxication and malaria infection in the monkey.

2. Ferrihemate-injected monkeys die in shock with the exhibition of symptoms suggestive of capillary blocking in vital organs, or recover very rapidly and completely after a brief interval of acute toxic reaction.

3. Ferrihemate is not a causative agent in the malaria paroxysm of monkeys since the pigment is not liberated in soluble form from the parasite.

## ACKNOWLEDGMENT

The study and observations on which this paper is based were aided by a grant from the Tennessee Valley Authority through the Department of Preventive Medicine of the University of Tennessee.

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## DEATHS DURING WEEK ENDED JANUARY 17, 1942

[From the Weekly Mortality Index, issued by the Bureau of the Census, Department of Commerce]

	Week ended Jan. 17, 1942	Correspond- ing week, 1941
Data from 87 large cities of the United States:		
Total deaths.....	9,594	9,604
Average for 3 prior years.....	9,248	
Total deaths, 2 weeks.....	19,292	19,325
Deaths per 1,000 population, 2 weeks, annual rate.....	13.6	13.6
Deaths under 1 year of age.....	553	541
Average for 3 prior years.....	536	
Deaths under 1 year of age, 2 weeks.....	1,204	1,103
Data from industrial insurance companies:		
Policies in force.....	64,887,805	64,741,173
Number of death claims.....	13,432	13,875
Death claims per 1,000 policies in force, annual rate.....	10.8	11.2
Death claims per 1,000 policies, 2 weeks, annual rate.....	10.1	10.7

## PREVALENCE OF DISEASE

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*No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring*

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### UNITED STATES

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#### REPORTS FROM STATES FOR WEEK ENDED JANUARY 24, 1942

##### Summary

Of the nine communicable diseases included in the weekly reports and for which comparable figures are available for earlier years, only measles, poliomyelitis, and whooping cough were above the 5-year (1937-41) median during the current week, and the incidence of these diseases was only slightly above the median expectancy.

The incidence of influenza continued low, with no evidence of a Nation-wide epidemic. A total of 4,332 cases was reported as compared with 3,894 for the preceding week, 91,203 for the corresponding week last year, and a 5-year (1937-41) median of 13,242 cases. In recent weeks the incidence of influenza has been constantly highest in a few of the South Atlantic and South Central States, which areas reported about 84 percent of the cases for the current week. Texas, where the disease has been mildly epidemic since the summer of last year, reported 1,553 cases for the current week; South Carolina, 653; Alabama, 433; and Virginia, 362. Only 6 other States reported 100 or more cases.

Ten States reported a total of 20 cases of smallpox (as compared with a 5-year median of 278 cases), and 89 cases of typhoid fever were reported, as compared with a median expectancy of 109 cases. Two cases of anthrax were reported (1 each in New Jersey and Pennsylvania), 19 cases of amebic dysentery (7 in California and 4 in Illinois), 72 cases of bacillary dysentery (59 in Texas), and 32 cases of tularemia. Fifty-one cases of endemic typhus fever were reported, all in the South Atlantic and South Central States.

The crude death rate for the week for 88 large cities in the United States was 13.0 per 1,000 population, as compared with 13.5 for the preceding week and 13.6 for the 3-year (1939-41) average. The accumulated rate for the first 3 weeks of 1942 is 13.4 as compared with 14.0 for the corresponding period last year.

*Telegraphic morbidity reports from State health officers for the week ended January 24, 1942, and comparison with corresponding week of 1941 and 5-year median*

In these tables a zero indicates a definite report, while leaders imply that, although none were reported, cases may have occurred.

Division and State	Diphtheria			Influenza			Measles			Meningitis, meningococcus		
	Week ended—		Median 1937- 41	Week ended—		Median 1937- 41	Week ended—		Median 1937- 41	Week ended—		Median 1937- 41
	Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941	
NEW ENG.												
Maine	0	0	4	1,138	34	261	34	96	1	0	0	
New Hampshire	0	0	0	44		7	15	15	0	0	0	
Vermont	0	0	0	23		10	38	22	0	0	0	
Massachusetts	3	3	4			284	341	341	1	0	1	
Rhode Island	1	0	0	1	29	88	2	2	0	1	0	
Connecticut	2	1	3	2	1,869	13	143	21	164	0	0	
MID. ATL.												
New York	20	18	28	111	1,522	137	346	2,125	400	3	4	5
New Jersey	8	22	15	10	377	32	167	688	467	2	1	1
Pennsylvania	17	6	36				1,214	2,485	131	3	4	8
E. NO. CEN.												
Ohio	7	8	29	29	3,245	21	96	770	39	2	2	2
Indiana	8	11	20	14	432	28	67	126	16	0	2	2
Illinois	24	14	33	34	171	79	104	1,210	45	1	0	0
Michigan	15	4	9	5	412	12	176	1,199	511	0	0	1
Wisconsin	3	1	1	20	230	64	179	286	286	0	3	1
W. NO. CEN.												
Minnesota	1	3	3	2	954	8	326	7	25	1	0	0
Iowa	3	5	5	1	671	22	62	109	78	0	0	0
Missouri	8	3	14	12	147	147	82	26	13	0	2	1
North Dakota	2	3	2	14	141	42	80	13	6	0	0	0
South Dakota	6	9	0		5	4	6	39	5	0	0	0
Nebraska	0	4	3		34		43	2	5	0	0	0
Kansas	2	1	7	17	750	142	135	223	213	1	1	0
SO. ATL.												
Delaware	3	1	1		392		7	20	8	1	1	0
Maryland	7	5	7	6	624	132	243	25	25	2	1	2
Dist. of Col.	3	1	4	3	168	19	17	5	5	1	0	0
Virginia	8	6	21	362	12,868	282	195	304	188	4	2	2
West Virginia	11	8	14	38	13,565	56	190	54	26	1	2	3
North Carolina	17	24	24	31	1,277	62	777	87	87	1	2	2
South Carolina	6	8	10	653	11,731	865	154	25	11	1	1	1
Georgia	10	2	11	101	9,031	470	130	63	52	0	0	0
Florida	9	1	8	8	216	50	49	6	33	1	1	1
E. SO. CEN.												
Kentucky	7	8	10	21	2,450	59	38	164	73	1	2	4
Tennessee	5	5	13	81	3,528	325	111	42	47	1	2	2
Alabama	20	5	13	433	7,043	399	72	81	81	2	2	2
Mississippi	8	2	6							0	1	1
W. SO. CEN.												
Arkansas	13	12	12	186	2,633	651	175	63	19	0	2	1
Louisiana	11	4	15	8	660	42	24	1	4	2	0	0
Oklahoma	10	9	9	138	1,521	373	183	5	5	0	1	1
Texas	71	23	44	1,553	7,830	2,158	1,097	102	195	9	3	0
MOUNTAIN												
Montana	0	3	0	9	721	33	54	3	3	0	0	0
Idaho	5	0	0		79	2	22	0	60	0	0	0
Wyoming	0	2	0	70	616		13	2	2	0	0	0
Colorado	6	1	7	77	603	27	190	57	57	0	0	0
New Mexico	0	0	0		159	21	53	84	49	1	0	1
Arizona	2	4	6	100	528	271	201	106	10	0	1	0
Utah	0	3	1	105	155	45	38	16	29	0	0	0
Nevada	0	0					0	0		0	0	
PACIFIC												
Washington	0	2	2	12	110	13	35	82	82	2	1	1
Oregon	1	0	2	53	125	116	223	22	0	1	1	1
California	16	17	24	112	1,376	1,376	1,621	83	110	7	2	1
Total	369	272	574	4,332	91,203	13,242	9,681	11,462	9,284	52	48	52
3 weeks	1,127	919	1,888	12,026	294,168	34,741	25,839	32,697	25,811	165	147	155

See footnotes at end of table.



Telegraphic morbidity reports from State health officers for the week ended January 24, 1942, and comparison with corresponding week of 1941 and 5-year median—Con.

Division and State	Poliomyelitis			Scarlet fever			Smallpox			Typhoid and para-typhoid fever		
	Week ended—		Med-ian 1937-41	Week ended—		Med-ian 1937-41	Week ended—		Med-ian 1937-41	Week ended—		Med-ian 1937-41
	Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941		Jan. 24, 1942	Jan. 25, 1941	
NEW ENG.												
Maine.....	0	0	0	26	5	17	0	0	0	0	1	1
New Hampshire.....	0	0	0	12	4	8	0	0	0	0	0	0
Vermont.....	0	0	0	7	11	11	0	0	0	0	0	0
Massachusetts.....	0	0	0	374	149	195	0	0	0	6	1	1
Rhode Island.....	0	0	0	33	4	8	0	0	0	0	0	0
Connecticut.....	0	0	0	38	39	75	0	0	0	0	1	1
MID. ATL.												
New York.....	2	2	1	350	440	584	0	0	0	6	2	5
New Jersey.....	2	0	0	112	269	146	0	0	0	0	0	0
Pennsylvania.....	3	2	0	278	283	500	0	0	0	6	2	6
E. NO. CEN.												
Ohio.....	3	1	2	320	247	300	0	0	3	4	1	2
Indiana.....	0	0	0	107	157	189	3	2	7	1	3	1
Illinois.....	2	2	1	265	410	489	2	0	21	2	8	7
Michigan <sup>1</sup> .....	3	4	0	399	187	574	0	4	0	1	2	2
Wisconsin.....	1	2	0	166	147	204	0	2	12	0	0	0
W. NO. CEN.												
Minnesota.....	0	0	0	106	56	139	2	3	13	0		0
Iowa.....	0	5	1	63	56	140	0	7	12	1		1
Missouri.....	1	0	0	86	91	174	3	6	18	0	1	1
North Dakota.....	1	0	0	44	3	21	1	0	2	0	0	0
South Dakota.....	1	0	0	49	29	26	0	0	0	0	0	0
Nebraska.....	0	0	0	38	20	36	1	0	0	0	0	0
Kansas.....	0	1	1	79	64	151	2	2	8	0	0	0
SO. ATL.												
Delaware.....	0	0	0	62	13	13	0	0	0	0	0	0
Maryland <sup>1</sup> .....	0	0	0	68	83	62	0	0	0	4	2	3
Dist. of Col.....	0	0	0	15	11	15	0	0	0	0	0	1
Virginia.....	0	0	0	52	50	50	0	0	0	3	2	3
West Virginia.....	0	0	0	91	33	60	0	0	0	1	2	1
North Carolina.....	2	1	0	53	46	46	0	0	0	1	0	1
South Carolina.....	0	1	1	14	6	7	0	0	0	1	0	2
Georgia.....	0	3	2	17	25	19	0	0	0	3	1	3
Florida.....	0	2	0	3	1	6	0	0	0	4	0	0
E. SO. CEN.												
Kentucky <sup>1</sup> .....	0	4	1	114	66	66	0	0	0	1	7	2
Tennessee.....	0	0	0	78	93	47	0	1	1	2	5	2
Alabama.....	1	0	1	37	19	18	0	0	0	4	3	3
Mississippi.....	0	0	0	13	7	7	0	2	1	0	2	1
W. SO. CEN.												
Arkansas.....	0	0	0	11	8	9	0	0	2	5	1	3
Louisiana.....	2	2	0	5	10	18	0	0	0	13	1	5
Oklahoma.....	0	0	1	15	27	43	0	0	0	2	3	2
Texas.....	1	1	1	82	54	97	4	2	5	10	0	10
MOUNTAIN												
Montana.....	0	0	0	20	24	30	0	0	3	0	1	1
Idaho.....	0	0	0	15	14	24	1	0	8	1	0	2
Wyoming.....	0	0	0	7	8	8	0	0	1	0	0	0
Colorado.....	0	0	0	24	29	36	0	12	8	1	2	0
New Mexico.....	0	0	0	2	6	23	0	2	1	0	2	2
Arizona.....	0	0	0	8	5	10	0	0	0	0	0	0
Utah <sup>1</sup> .....	1	1	0	35	6	28	0	0	0	0	0	0
Nevada.....	0	0	0	0	0	0	0	0	0	0	3	0
PACIFIC												
Washington.....	1	1	1	32	27	61	1	1	1	2	2	0
Oregon.....	0	0	1	19	12	46	0	0	5	1	0	0
California.....	1	2	1	128	112	221	0	1	10	3	1	5
Total.....	28	37	24	3,981	3,466	5,492	20	47	78	89	67	109
3 weeks.....	85	103	71	10,374	10,004	15,238	41	152	869	243	232	329

See footnotes at end of table.

*Telegraphic morbidity reports from State health officers for the week ended January 24, 1942,—Continued*

Division and State	Whooping cough, week ended—		Week ended Jan. 24, 1942									
	Jan. 24, 1942	Jan. 25, 1941	Anthrax	Dysentery			Encephalitis, infectious	Leprosy	Rocky Mt. spotted fever	Tularemia	Typhus fever	
				Amebic	Bacillary	Unspecified						
NEW ENG.												
Maine.....	52	18	0	0	0	0	0	0	0	0	0	0
New Hampshire.....	5	0	0	0	0	0	0	0	0	0	0	0
Vermont.....	33	17	0	0	0	0	0	0	0	0	0	0
Massachusetts.....	296	250	0	0	0	0	0	0	0	0	0	0
Rhode Island.....	92	6	0	0	0	0	0	0	0	0	0	0
Connecticut.....	135	89	0	0	3	0	0	0	0	0	0	0
MID. ATL.												
New York.....	578	351	0	0	0	0	0	0	0	0	0	0
New Jersey.....	257	126	1	0	0	0	0	0	0	0	0	0
Pennsylvania.....	330	494	1	0	0	0	0	0	0	0	0	0
E. NO. CEN.												
Ohio.....	306	332	0	1	0	0	0	0	0	1	0	0
Indiana.....	52	22	0	0	0	0	0	0	0	0	0	0
Illinois.....	286	108	0	4	1	0	0	0	1	1	0	0
Michigan <sup>2</sup> .....	434	331	0	1	1	0	0	0	0	0	0	0
Wisconsin.....	364	149	0	0	0	0	0	0	0	0	0	0
W. NO. CEN.												
Minnesota.....	27	49	0	0	0	0	0	0	0	1	0	0
Iowa.....	28	15	0	0	0	0	0	0	0	1	0	0
Missouri.....	11	42	0	0	0	0	0	0	0	0	0	0
North Dakota.....	21	32	0	0	0	0	1	0	0	0	0	0
South Dakota.....	5	3	0	0	0	0	0	0	0	0	0	0
Nebraska.....	9	2	0	0	0	0	0	0	0	0	0	0
Kansas.....	61	93	0	0	0	0	0	0	0	1	0	0
SO. ATL.												
Delaware.....	0	21	0	0	0	0	0	0	0	0	0	0
Maryland <sup>2</sup> .....	41	87	0	0	0	1	0	0	0	2	0	0
Dist. of Col.....	26	7	0	0	0	0	0	0	0	0	0	0
Virginia.....	45	128	0	1	0	28	0	0	0	1	0	0
West Virginia.....	79	55	0	0	0	0	0	0	0	0	0	0
North Carolina.....	250	218	0	0	0	0	0	0	0	2	2	0
South Carolina.....	41	120	0	0	0	0	0	0	0	3	4	0
Georgia.....	16	26	0	1	5	0	0	0	0	4	12	0
Florida.....	27	7	0	0	0	0	0	0	0	0	2	0
E. SO. CEN.												
Kentucky <sup>2</sup> .....	94	46	0	0	1	0	0	0	0	5	0	0
Tennessee.....	18	64	0	1	0	1	0	0	0	7	0	0
Alabama.....	9	26	0	0	0	0	0	0	0	0	0	10
Mississippi.....			0	0	0	0	0	0	0	1	0	0
W. SO. CEN.												
Arkansas.....	14	24	0	1	0	0	0	0	0	0	0	0
Louisiana.....	1	7	0	0	0	0	0	0	0	0	5	0
Oklahoma.....	13	20	0	0	0	0	0	0	0	0	0	0
Texas.....	92	249	0	2	59	0	0	0	0	0	0	16
MOUNTAIN												
Montana.....	16	15	0	0	0	0	1	0	0	0	0	0
Idaho.....	8	18	0	0	0	0	0	0	0	1	0	0
Wyoming.....	0	0	0	0	0	0	0	0	0	1	0	0
Colorado.....	41	34	0	0	0	0	0	0	0	0	0	0
New Mexico.....	50	39	0	0	0	0	1	0	0	0	0	0
Arizona.....	54	10	0	0	0	7	0	0	0	0	0	0
Utah <sup>2</sup> .....	54	57	0	0	0	0	0	0	0	0	0	0
Nevada.....	2	0	0	0	0	0	0	0	0	0	0	0
PACIFIC												
Washington.....	169	96	0	0	0	0	0	0	0	0	0	0
Oregon.....	54	16	0	0	0	0	0	0	0	0	0	0
California.....	222	318	0	7	2	0	1	0	0	0	0	0
Total.....	4,818	4,237	2	19	72	37	4	0	1	32	51	
3 weeks.....	12,546	13,561										

<sup>1</sup> New York City only.<sup>2</sup> Period ended earlier than Saturday.<sup>3</sup> Inclusive of delayed reports as follows: Diphtheria, 1; influenza, 21; measles, 1; scarlet fever, 4.

## WEEKLY REPORTS FROM CITIES

City reports for week ended January 10, 1942

This table lists the reports from 88 cities of more than 10,000 population distributed throughout the United States, and represents a cross section of the current urban incidence of the diseases included in the table.

	Diph- theria cases	En- ceph- alitis, infectious cases	Influenza		Meas- les cases	Men- ingit- is, men- ingo- coccus, cases	Pneu- monia deaths	Polio- mye- litis cases	Scar- let fever cases	Small- pox cases	Ty- phoid and para- ty- phoid fever cases	Whoop- ing cough cases
			Cases	Deaths								
Atlanta, Ga.	1	0	8	2	5	0	3	0	10	0	0	0
Baltimore, Md.	3	0	8	3	218	2	21	0	15	0	0	9
Barre, Vt.	0	0	0	0	1	0	0	0	1	0	0	0
Billings, Mont.	0	0	0	0	0	0	1	0	1	0	0	0
Birmingham, Ala.	0	0	1	1	0	0	6	0	4	0	0	1
Boise, Idaho	0	0	0	0	0	0	0	0	0	0	0	0
Boston, Mass.	2	0	0	0	59	2	12	0	100	0	0	35
Bridgeport, Conn.	0	0	0	1	2	0	1	0	1	0	0	2
Brunswick, Ga.	0	0	0	0	4	0	0	0	0	0	0	0
Buffalo, N. Y.	0	0	0	0	1	0	6	0	22	0	1	12
Camden, N. J.	0	0	0	0	4	0	2	0	2	0	0	10
Charleston, S. C.	0	0	34	2	0	0	9	0	1	0	0	2
Charleston, W. Va.	0	0	1	0	2	0	3	0	1	0	0	0
Chicago, Ill.	23	0	7	2	14	0	38	0	94	0	0	84
Cincinnati, Ohio	0	0	0	2	0	0	7	0	20	0	0	29
Cleveland, Ohio	1	0	20	2	7	1	20	0	48	0	0	34
Columbus, Ohio	0	0	0	0	5	0	3	0	2	0	0	3
Concord, N. H.	0	0	0	0	0	0	0	0	3	0	0	0
Cumberland, Md.	0	0	0	0	2	0	0	0	0	0	0	0
Dallas, Tex.	5	0	2	1	52	0	1	0	6	0	0	3
Denver, Colo.	6	0	42	0	42	0	5	0	3	1	0	11
Detroit, Mich.	5	0	1	2	17	0	15	1	82	0	0	47
Duluth, Minn.	0	0	0	0	3	0	2	0	6	0	0	1
Fall River, Mass.	0	0	0	0	0	0	0	0	27	0	0	2
Fargo, N. Dak.	0	0	0	0	0	0	1	0	0	0	0	0
Flint, Mich.	0	0	0	0	0	0	5	0	1	0	0	5
Fort Wayne, Ind.	0	0	0	0	0	0	3	0	1	0	0	0
Frederick, Md.	0	0	0	0	0	0	0	0	0	0	0	0
Galveston, Tex.	1	0	0	0	1	0	0	0	2	0	0	0
Grand Rapids, Mich.	0	0	0	0	11	0	1	0	4	0	0	7
Great Falls, Mont.	0	0	0	0	25	0	1	0	1	0	0	6
Hartford, Conn.	0	0	0	1	0	0	1	0	1	0	0	2
Helena, Mont.	0	0	0	0	0	0	0	0	0	0	0	4
Houston, Tex.	5	0	0	0	2	0	15	0	8	0	2	0
Indianapolis, Ind.	0	0	0	0	6	0	8	0	7	0	0	22
Kansas City, Mo.	0	0	0	0	5	0	2	0	10	0	0	4
Kenosha, Wis.	0	0	0	0	2	0	0	0	2	0	0	5
Little Rock, Ark.	0	0	8	0	6	0	1	0	0	0	0	2
Los Angeles, Calif.	4	0	38	1	39	1	15	0	15	0	0	17
Lynchburg, Va.	0	0	0	0	0	0	1	0	1	0	0	0
Memphis, Tenn.	0	0	12	4	2	0	1	0	3	0	0	8
Milwaukee, Wis.	0	0	0	0	12	2	0	0	25	0	0	80
Minneapolis, Minn.	1	0	0	0	3	0	4	0	13	0	0	0
Missoula, Mont.	0	0	0	0	0	0	0	0	0	0	0	5
Mobile, Ala.	0	1	0	1	8	0	2	0	0	0	0	0

## City reports for week ended January 10, 1942—Continued

	Diph- theria cases	En- ceph- alitis, infec- tious cases	Influenza		Mea- sles cases	Men- ing- tis, men- ingo- coccus cases	Pneu- monia deaths	Polio- mye- litis cases	Scar- let fever cases	Small- pox cases	Ty- phoid and para- ty- phoid fever cases	Whoop- ing cough cases
			Cases	Deaths								
Nashville, Tenn.	0	0	-----	1	1	0	3	0	3	0	0	1
Newark, N. J.	0	0	10	1	48	2	5	1	17	0	0	20
New Haven, Conn.	0	0	-----	0	43	0	1	0	2	0	0	5
New Orleans, La.	0	0	1	1	1	0	20	0	4	0	2	1
New York, N. Y.	15	1	8	2	28	5	84	0	159	0	2	330
Omaha, Nebr.	1	0	-----	0	2	0	4	0	0	0	0	1
Philadelphia, Pa.	7	0	2	1	12	1	24	0	97	0	0	65
Pittsburgh, Pa.	1	0	2	0	15	1	11	0	12	0	0	8
Portland, Maine	0	0	-----	0	2	0	6	0	11	0	0	2
Providence, R. I.	1	0	-----	0	10	0	5	0	9	0	0	47
Pueblo, Colo.	0	0	-----	0	129	0	1	0	2	0	0	0
Racine, Wis.	0	0	-----	0	13	0	0	0	1	0	0	10
Reading, Pa.	0	0	-----	0	4	0	1	0	0	0	0	4
Richmond, Va.	0	0	2	2	0	0	4	0	2	0	1	0
Roanoke, Va.	0	0	-----	0	1	0	0	0	0	0	0	0
Rochester, N. Y.	0	0	-----	0	4	0	2	0	5	0	0	14
Sacramento, Calif.	1	0	-----	0	87	0	2	0	8	0	0	2
Saint Joseph, Mo.	0	0	-----	0	3	0	6	0	1	0	0	0
Saint Louis, Mo.	0	0	2	2	15	0	14	0	16	0	0	9
Saint Paul, Minn.	0	1	-----	0	119	0	1	0	3	0	0	13
San Antonio, Tex.	1	0	9	2	1	0	9	0	0	0	0	7
San Francisco, Calif.	0	0	3	0	9	1	10	0	4	0	0	2
Savannah, Ga.	0	0	7	1	34	0	2	0	2	0	0	1
Seattle, Wash.	0	0	-----	0	0	0	4	0	1	0	0	17
Shreveport, La.	3	0	-----	7	1	0	3	0	0	0	0	0
South Bend, Ind.	0	0	-----	0	1	0	2	0	5	0	0	0
Spokane, Wash.	0	0	-----	0	4	0	2	0	6	0	0	12
Springfield, Ill.	2	0	-----	0	0	0	1	0	1	0	0	1
Springfield Mass.	0	0	-----	0	15	0	6	0	15	0	0	41
Superior, Wis.	0	0	-----	0	1	0	0	1	0	0	0	10
Syracuse, N. Y.	0	0	-----	0	1	0	2	0	2	0	0	37
Tacoma, Wash.	0	0	-----	0	0	0	3	0	3	0	0	2
Tampa, Fla.	0	0	1	1	0	0	2	0	0	0	0	1
Terre Haute, Ind.	0	0	-----	0	0	0	1	0	0	0	0	0
Topeka, Kans.	0	0	-----	0	2	0	0	0	6	0	0	6
Trenton, N. J.	0	0	3	0	0	0	3	0	4	0	0	7
Washington, D. C.	0	0	6	0	5	0	13	0	14	0	0	38
Wheeling, W. Va.	0	0	-----	0	49	0	1	0	4	0	0	0
Wichita, Kans.	0	0	1	1	15	0	3	0	7	0	0	5
Wilmington, Del.	1	0	-----	0	1	0	5	0	19	0	0	0
Wilmington, N. C.	0	0	-----	0	68	0	2	0	0	0	0	1
Winston-Salem, N. C.	1	0	-----	0	36	0	1	0	6	0	0	0
Worcester, Mass.	0	0	-----	0	1	0	5	0	20	0	0	24

*Rates (annual basis) per 100,000 population for a group of 88 selected cities (population, 1941, 33,774,582)*

Period	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Typhoid fever cases	Whooping cough cases
		Cases	Deaths						
Week ended Jan. 10, 1942....	14.00	36.77	7.23	203.47	75.84	156.01	0.15	1.23	184.01
Average for week, 1937-41....	20.65	337.59	17.55	323.45	122.36	193.17	4.04	3.11	165.07



## FOREIGN REPORTS

### BRITISH EAST AFRICA

*Tanganyika Territory—Cerebrospinal meningitis.*—Cerebrospinal meningitis has been reported in Tanganyika Territory, British East Africa, by weeks, as follows:

Week ended—	Cases	Deaths	Week ended—	Cases	Deaths
1941			1941		
Oct. 4 .....	153	9	Nov. 1 .....	134	20
Oct. 11 .....	255	35	Nov. 8 .....	328	175
Oct. 18 .....	192	36	Nov. 15 .....	76	11
Oct. 25 .....	225	31	Nov. 22 .....	101	29

NOTE.—See also PUBLIC HEALTH REPORTS for Dec. 19, 1941, p. 2442.

### CANADA

*Provinces—Communicable diseases—Week ended December 27, 1941.*—During the week ended December 27, 1941, cases of certain communicable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Que- bec	On- tario	Mani- toba	Sas- katch- ewan	Al- berta	British Colum- bia	Total
Cerebrospinal meningitis.....				4	6	1			3	14
Chickenpox.....				136	288	69	109	36	49	687
Diphtheria.....		27		15	4	6	1		3	56
Dysentery.....				3	2					5
Influenza.....		3			3	7			54	67
Measles.....		2		437	51	67	40	9	16	622
Mumps.....		4	1	288	189	55	31	25	72	665
Pneumonia.....		1			6	3			12	22
Poliomyelitis.....		1						1		2
Scarlet fever.....		13	10	118	217	16	12	31	11	428
Trachoma.....						1				1
Tuberculosis.....			3	91	31	24		1		150
Typhoid and paraty- phoid fever.....				12		3				15
Whooping cough.....		5	1	44	56	5		2	16	129

# WORLD DISTRIBUTION OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER

From medical officers of the Public Health Service, American consuls, International Office of Public Health, Pan American Sanitary Bureau, health section of the League of Nations, and other sources. The reports contained in the following tables must not be considered as complete or final as regards either the list of countries included or the figures for the particular countries for which reports are given.

## CHOLERA

[C indicates cases]

NOTE.—Since many of the figures in the following tables are from weekly reports, the accumulated totals are for approximate dates.

Place	January- October 1941	November 1941	December 1941—week ended—			
			6	13	20	27
ASIA						
Afghanistan: Southern Province. <sup>1</sup>						
Ceylon.....	C	3				
China:						
Canton.....	C	464				
Hong Kong.....	C	1,659				
Macao.....	C	1,411	62	2		
Shanghai.....	C	812	22			
India.....	C	87,896				
Bombay.....	C	15				
Calcutta.....	C	2,069	50			
Rangoon.....	C	116				
India (French).....	C	34				
Japan: Taiwan.....	C	2				

<sup>1</sup> During the week ended Dec. 6, 1941, cholera was reported present in Southern Province, Afghanistan.

## PLAGUE

[C indicates cases; P, present]

<b>AFRICA</b>						
Belgian Congo.....	C	139				
British East Africa:						
Kenya.....	C	589	97			
Tanganyika Territory.....	C	2				
Uganda.....	C	153	26			
Egypt: Port Said.....	C	10				
Madagascar.....	C	229	19			37
Morocco.....	C	2,127	45	15	5	5
Casablanca <sup>1</sup> .....	C	4	3			4
Tunisia: Tunis.....	C	2				
Union of South Africa.....	C	71	2			
<b>ASIA</b>						
China:						
Fukien Province. <sup>4</sup>						
Foochow.....	C	3				
Dutch East Indies:						
Java and Madura.....	C	459				
West Java.....	C	344				
India.....	C	3,975				
Calcutta.....	C	3				
Rangoon.....	C	9			P	
Indochina (French).....	C	24	1			
Palestine: Haifa.....	C	10	1			
Plague-infected rats.....	C	25				
Thailand: Lampang Province.....	C	3				
<b>EUROPE</b>						
Portugal: Azores Islands.....	C	2		1		
<b>NORTH AMERICA</b>						
Canada—Alberta—Plague-infected ground squirrels.....		1				
<b>SOUTH AMERICA</b>						
Argentina:						
Cordoba Province.....	C	21			P	
Lobos.....	C				2	
Santa Fe Province—Plague-infected rats.....		67				

<sup>1</sup> Includes 21 cases of pneumonic plague.

<sup>2</sup> For the month of December.

<sup>3</sup> A report dated June 23, 1941, stated that an outbreak of plague had occurred in Casablanca, Morocco, where several deaths had been reported.

<sup>4</sup> A report dated Nov. 22, 1941, stated that bubonic plague had appeared in epidemic form in Shaowu and Yangkow, Fukien Province.

<sup>5</sup> Includes 3 cases of pneumonic plague.

## PLAGUE—Continued

Place	January- October 1941	Novem- ber 1941	December 1941—week ended—			
			6	13	20	27
SOUTH AMERICA—continued						
Brazil:						
Alagoas State.....	C	36				
Bahia State.....	C	10				
Pernambuco State.....	C	70				
Rio de Janeiro State.....	C	2				
Chile: Valparaiso.....	C	1				
Ecuador.....	C	33				
Peru:						
Ancash Department.....	C	1	9			
Lambayeque Department.....	C	3				
Libertad Department.....	C	7	4			
Lima Department.....	C	15	2			
Moquegua Department—Ilo.....	C	7				
Piura Department.....	C	2	8			
OCEANIA						
Hawaii Territory: <sup>1</sup> Plague-infected rats.....		55	8			
New Caledonia.....	C	9	2			

<sup>1</sup> During April and May, 4 lots of plague-infected fleas were also reported in Hawaii Territory.

## SMALLPOX

[C Indicates cases]

AFRICA							
Algeria.....	C	548	199				
Angola.....	C	129					
Belgian Congo.....	C	673					
British East Africa.....	C	30	42				
Dahomey.....	C	467					
French Guinea.....	C	45					
Gold Coast.....	C	312					
Ivory Coast.....	C	40					
Morocco.....	C	648					
Nigeria.....	C	901					
Niger Territory.....	C	267					
Portuguese East Africa.....	C	9					
Rhodesia: Southern.....	C	86					
Senegal.....	C	65					
Sierra Leone.....	C	15					
Sudan (Anglo-Egyptian).....	C	7					
Sudan (French).....	C	19					
Union of South Africa.....	C	758					
ASIA							
Ceylon.....	C	114					
China.....	C	256	3				
Chosen.....	C	696					
Dutch East Indies—Bali Island.....	C	3					
India.....	C	23,928					
India (French).....	C	9					
India (Portuguese).....	C	70					
Indochina (French).....	C	1,123	45				4117
Iran.....	C	8					
Iraq.....	C	1,252	165				
Japan.....	C	200					
Straits Settlements.....	C	1					
Syria.....	C	1					
Thailand.....	C	303					
EUROPE							
France.....	C	1					
Portugal.....	C	39	2		2		
Spain.....	C	351	67	11	7		
Switzerland.....	C		1				
NORTH AMERICA							
Canada.....	C	25					
Dominican Republic.....	C	2					
Guatemala.....	C	5	1				
Mexico.....	C	317					
Panama Canal Zone (alastrim).....	C	1					

<sup>1</sup> For June.<sup>2</sup> A report dated Dec. 31, 1941, stated that an epidemic of smallpox had occurred near Casablanca, Morocco, where about 100 cases per week were reported.<sup>3</sup> For September.<sup>4</sup> For December.

## SMALLPOX—Continued

Place	January- October 1941	November 1941	December 1941—week ended—			
			6	13	20	27
SOUTH AMERICA						
Bolivia.....	C	18				
Brazil.....	C	1				
Colombia.....	C	716	2			
Paraguay.....	C	8				
Peru.....	C	778				
Uruguay.....	C	7				
Venezuela (alastrim).....	C	229	2			

<sup>1</sup> For January, February, and March.

<sup>2</sup> For August.

## TYPHUS FEVER

[C indicates cases]

<b>AFRICA</b>							
Algeria.....	C	10,083	637				
British East Africa: Kenya.....	C	6	4				
Egypt.....	C	8,632					
Morocco <sup>1</sup> .....	C	909	140		67	102	121
Sierra Leone.....	C	5					
Tunisia.....	C	5,114	926	186	168		275
Union of South Africa.....	C	438	15				
<b>ASIA</b>							
China.....	C	245					
Chosen.....	C	425					
Dutch East Indies: Sumatra.....	C	136					
India.....	C	4					
Iran.....	C	105					
Iraq.....	C	50	3				
Japan.....	C	864					
Malaya: Unfederated States.....	C	1					
Palestine.....	C	108	47				
Straits Settlements.....	C	7	1				
Trans-Jordan.....	C	9					
<b>EUROPE</b>							
Bulgaria.....	C	227	3	1		4	24
France (unoccupied zone).....	C	2					
Germany.....	C	1,771	119		27		
Gibraltar.....	C	2					
Greece.....	C	7					
Hungary.....	C	433	8				31
Irish Free State.....	C	26					
Poland.....	C	960					
Portugal.....	C	5					
Rumania.....	C	792	327		234	171	189
Spain.....	C	9,175	102	34	39		
Switzerland.....	C	5					
Turkey.....	C	645					
Yugoslavia.....	C	78					
<b>NORTH AMERICA</b>							
Guatemala.....	C	168	13				
Mexico.....	C	171					
Panama Canal Zone.....	C	3					
Puerto Rico.....	C	8	2			1	1
<b>SOUTH AMERICA</b>							
Bolivia.....	C	75					
Brazil.....	C	1					
Chile.....	C	276					
Colombia.....	C	1					
Ecuador.....	C	119					
Peru.....	C	1,079					
Venezuela.....	C	47	11				
<b>OCEANIA</b>							
Australia.....	C	12					
Hawaii Territory.....	C	47	0	3			

<sup>1</sup> Information dated Dec. 31, 1941, reports typhus fever present in epidemic form in Casablanca, Morocco.

<sup>2</sup> For January, February, and March.

<sup>3</sup> Jan. 1 to Aug. 3, 1941.

<sup>4</sup> January to June inclusive.

<sup>5</sup> For December.

## YELLOW FEVER

[C indicates cases; D, deaths]

Place		January- October 1941	November 1941	December 1941—week ended—			
				6	13	20	27
AFRICA							
Belgian Congo:							
Aba	C				12		
Kimvulu	C	1					
Libenge	C	1					
Stanleyville	D		11				
British East Africa: Uganda	C	1					
Dahomey: Grand-Popo	C					12	
French Equatorial Africa:							
Gabon	C	2					
Mayumba	C	4					
French Guinea	C		3				
French West Africa	C		5				
Gold Coast	C	2	11				
Accra	C	1					
Ivory Coast <sup>1</sup>	C	37		11			
Nigeria	C	11					
Spanish Guinea	D	4					
Sudan (French)	C		10	11			
SOUTH AMERICA <sup>2</sup>							
Brazil:							
Amazonas State	D	4					
Bahia State	D	2					
Para State	D	8					
Colombia:							
Antioquia Department	D	2	1				
Boyaca Department	D	8					
Intendencia of Meta	D	8	5				
Santander Department	D	17	2				
Tolima Department	D	1					
Peru: Junin Department	C	5					
Venezuela: Bolivar State	C	1					

<sup>1</sup> Suspected.<sup>2</sup> Includes 1 suspected case.<sup>3</sup> Includes 2 suspected cases.<sup>4</sup> During the week ended Jan. 10, 1942, 1 suspected case of yellow fever was reported in Azagule, Ivory Coast.<sup>5</sup> Includes 4 suspected cases.<sup>6</sup> All yellow fever reported in South America is of the jungle type unless otherwise specified.COURT DECISION ON PUBLIC HEALTH <sup>1</sup>

*Payment for services performed by superintendent of county board of health.*—(South Dakota Supreme Court; *Donahoe v. Minnehaha County*, 299 N.W. 238; decided July 3, 1941.) An action was brought by the plaintiff to recover for services performed by him as superintendent of a county board of health. The county had disallowed claims of the plaintiff based upon the making of routine examinations of school houses throughout the county. The judgment of the trial court was in favor of the defendant county and the plaintiff appealed to the supreme court.

The latter court referred to a statute which provided that a county board of health "shall have original power to inquire into sanitary conditions of school houses within the county, and upon complaint

<sup>1</sup> Through inadvertence only a partial abstract of this decision was published in Public Health Reports, Nov. 7, 1941, pp. 2187-2188. A complete abstract appears herein.



and investigation shall have power to abate any insanitary condition that may be found to exist." "In order," said the court, "that 'original power' may be exercised there must be some action by the board itself. \* \* \* Clearly the superintendent must receive some authority from the board of which he is a member before the investigations and services are rendered." It was pointed out that the record disclosed that none of the items for which the plaintiff sought recovery was authorized or directed to be done at any meeting of the county board of health and that there had been no authorization or direction by the board or anyone to incur the services, mileage, and expenses. Also, the record was silent as to the report of any immediate emergency. On account of the foregoing, the court did not believe that the plaintiff's claims should be allowed.

However, it was urged that, under another statutory provision, the action of the county board of health as such was not necessary and that the superintendent was entitled to his pay if he acted under the rules and regulations adopted by the State board of health. This statute provided that for each investigation, visit, or examination necessarily made under the provisions of the rules and regulations of the State board of health the superintendent of the county board of health should receive \$5. The rule of the State board upon which the plaintiff relied read: "When it shall come to the attention of the health officer by complaint or otherwise that a school premises be in an insanitary condition, and he finds that existing conditions warrant, he shall forthwith order that the place be closed and kept closed until it has been repaired and properly disinfected or cleansed, or both, as the case may require." The appellate court said that it was convinced that the routine examinations of the school premises made by the plaintiff did not come within the meaning of the above quoted regulation of the State board. No complaint had been made to the plaintiff regarding the insanitary condition of any school, and the examinations were not made because he had been in any way advised that any school was in an insanitary condition. "It is clear under the evidence in this case that insanitary conditions in any school house in the county had not come to the attention of the appellant but that the examinations he made were routine examinations not based upon any belief that insanitary conditions actually existed!" The court was, therefore, of the opinion that it need not decide the contention that the State board of health by regulation could compel the superintendent of the county board of health to act and that when he did act under such regulation without the sanction of the county board there was a liability incurred by the county for such acts.

The judgment of the trial court was affirmed.